Design, Preparation, and Biodistribution of a Technetium-99m Triaminedithiol Complex to Assess Regional Cerebral Blood Flow

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A new ligand (N-piperidinylethyl-DADT, 5) has been prepared which forms two complexes with ^{99m}Tc when stannous chloride is used as a reducing agent for [^{99m}Tc] pertechnetate. Biodistribution studies of one of the complexes in mice showed that 2.2% of the injected dose of the tracer was in the brain at 5 min postintravenous injection with 0.53% of the dose remaining in the brain at 30 min postinjection. Brain-to-blood ratios at these times were 5.3 and 3.0, respectively. Biodistribution studies of the other complex showed similar behavior with a slightly lower initial uptake by and faster clearance from the brain. Imaging studies of the more promising of the two complexes were conducted in a monkey and a baboon. In both cases, rapid uptake of the tracer in the brain was observed and clear brain images were obtained. Time-activity curves showed peak uptake in the brain at ~ 5 to 7 min postintravenous injection followed by a plateau of about 11 min. The half-lives for clearance of the tracer from the brains of the monkey and baboon were found to be 63 and 58 min, respectively. These results suggest that this tracer may be useful for brain imaging in humans.

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The design of brain perfusion agents continues as an area of nuclear medicine research which is receiving much attention. Such an agent must be capable of freely crossing the blood-brain barrier and must be sufficiently retained by the brain to permit meaningful images to be obtained. Several radiolabeled amines, including selenium-75 (^{75}Se) PIPSE, [^{75}Se]MOSE (*1,2*), iodine-123 N-isopropyl-iodoamphetamine ([^{123}I] IMP) (*3*) and [^{123}I]HIPDM (*4, 5*) (Fig. 1) possess these characteristics. Two of these, [^{123}I] IMP and [^{123}I]HIPDM are currently undergoing clinical trials (*6*). Although several mechanisms have been proposed for the retention of these compounds by the brain, none has yet been clearly established (*2,7*). The poor physical characteristics of ^{75}Se, high cost of ^{123}I, and the contamination of currently produced ^{123}I with amounts of ^{124}I, suggest that the development of alternative agents would be desirable.

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As part of an ongoing program to develop useful radiopharmaceuticals containing technetium, we have investigated a number of ligand systems for complexation with technetium (*8-10*). From this work, we have determined that ligands based on the diaminedithiol (DADT) backbone (*11*) give complexes (Fig. 2) which are stable, neutral, and lipid-soluble (*12-14*). In addition, they have been shown to cross the blood-brain barrier (*15*); however, they are not retained by the brain for a time period which would permit single photon emission computed tomography (SPECT) scanning (*16*) with currently available instrumentation.

This paper describes the design, synthesis, and preliminary evaluation in experimental animals of a technetium 99m (^{99m}Tc) complex of a DADT ligand functionalized with a piperidinylethyl side chain (Fig. 3) (N-piperidinylethyl-DADT, 5). The design of this complex was based on the combination of observations that ^{99m}Tc complexes of DADT ligands are capable of crossing the blood-brain barrier and that some alkylamines (e.g., [^{75}Se]PIPSE) accumulate and are retained by the brain for sufficient time

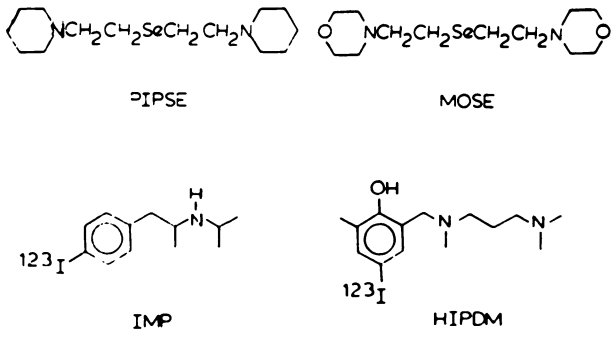

FIGURE 1
Structures of PIPSE, MOSE, IMP, and HIPDM

periods to permit one to obtain images which reflect the distribution of regional cerebral blood flow.

MATERIALS AND METHODS

Experimental chemistry

The organic compounds synthesized were characterized by melting point*, ^{1}H-NMR† and IR‡ spectroscopy, and elemental analysis§. Analysis of ^{99m}Tc labeling reactions were performed using high performance liquid chromatography (HPLC)¶ utilizing reverse phase columns**, a calcium fluoride radiodetector, and uv monitor††.

Preparation of 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclo-deca-4,8-diene (1)

To a stirred solution of 2,2′-dithio-bis(2 methylpropanal (*17*) (0.1430 mol, 29.12 g) in benzene (280 ml) containing tosic acid (50 mg), 2-methyl-1,2-diaminopropane (0.1430 mol, 12.60 g) was added dropwise. The reaction mixture was refluxed with azeotropic removal of water (2 hr); the solvent was then removed under reduced pressure. The residue was triturated with low boiling petroleum ether and triturant was treated with decolorizing charcoal. The solution was concentrated until crystals began to form. The crystals were collected by filtration, and washed with cold petroleum ether (50 ml) to afford a pale yellow product: 21.72 g (58.8%). An additional recrystallization yielded white crystals for analysis (mp 97-99°C); IR (KBr) 1640 cm^{-1}, (C=N). NMR ($CDCl_3$) δ 1.25-1.42 (18H); 2.82-2.94 (1H); 3.69-3.82 (1H), 6.83-6.89 (2H).

Anal. Calcd. for $C_{12}H_{22}N_2S_2$: C, 55.77; H, 8.58; N, 10.84; S, 24.81.
Found: C, 55.88; H, 8.68; N, 10.79; S, 24.99.

Preparation of 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodecane (2)

To a solution of 1 (150.43 g, 0.5822 mole) dissolved in warm absolute EtOH (1800 ml), sodium borohydride (22.00 g, 0.5815 mole) was slowly added. After 2 hr of stirring at room temperature, acetone (150 ml) was added. After stirring for 20 min, the solvent was removed under reduced pressure. To the residue, pentane (600 ml) was added and the resulting mixture was filtered and the filtrate was evaporated to dryness. A small portion of the crude mixture (3.00 g) was purified by column chromatography (basic alumina; gradient elution with pentane/ether/ethyl acetate mixtures.) Four components were isolated (shown to be isomeric by elemental analysis, and characterized by ^{1}H-NMR, but not carried any further.) The fraction isolated is the only reactive species towards acylation (in subsequent reactions, the crude reaction mixture was used): 1.34 g, 47.7%, white solid, mp 71-4°C; TLC (Silica gel/EtOAc): R_f 0.47. IR (free base, KBr) 3225 cm^{-1} (NH). NMR (free base, $CDCl_3$) δ 1.00-1.38 (m, 19H; 18H after D_2O addition); 2.07 (m, 2H; s, 1H after D_2O addn); 2.67-2.71 (m, 4H); 3.56 (s, 1H).

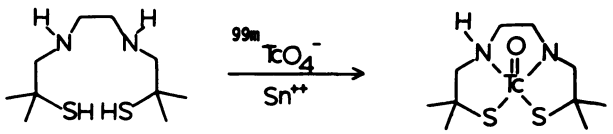

FIGURE 2
Structure of diaminedithiol ^{99m}Tc complex

Anal. Calcd for $C_{12}H_{26}N_2S_2$: C, 54.91; H, 9.98; N, 10.67; S, 24.44.
Found: C, 55.34; H, 9.29; N, 10.75; S, 24.58.

Preparation of 5-chloroacetyl-3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodecane (3)

Chloroacetyl chloride (22.06 g, 0.1953 mole) was added over a 20 min. time period to a solution of diamine 2 (isomeric mixture) (73.22 g, 0.2790 mole) in diethyl ether (400 ml). A white precipitate formed immediately, and after 1 hr at room temperature, the reaction mixture was filtered. The solids were washed with warm ether and the ether solution was concentrated affording a pale yellow precipitate (49.49 g, 52.34%): mp 116-119°C. An analytical sample was obtained by recrystallization from diethyl ether (mp 122-125°C). IR (KBr) 1660 cm^{-1} (C=O). NMR ($CDCl_3$ δ 0.97-1.38 (m, 19H); 2.77 (s, 2H); 3.25-3.46 (m, 3H); 4.01 (s, 2H); 4.75 (br s, 1H).

Anal. Calcd for $C_{14}H_{27}ClN_2S_2O$: C, 49.61; H, 8.03; Cl, 10.46; N, 8.26; S, 18.92.
Found: C, 49.63; H, 7.21; Cl, 10.84; N, 8.22; S, 18.92.

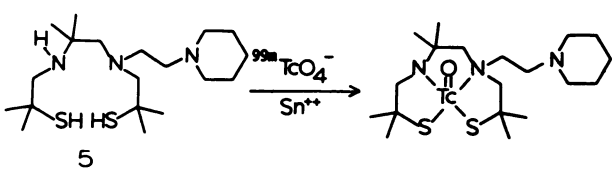

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FIGURE 3
Proposed structure of triaminedithiol ^{99m}Tc complex

Preparation of 5-(2′-piperidinylacetyl)-3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodecane (4)

Piperidine (18.58 g, 0.2182 ml) was added dropwise to a solution of **3** (100 g, 0.0295 mole) in absolute EtOH (50 ml). The mixture was heated at reflux for 2 hr (the reaction was monitored by thin layer chromatography (TLC) for the disappearance of starting material). Volatiles were removed under reduced pressure. The pH of the residue was adjusted to 11 with 0.1*N* NaOH and extracted with diethyl ether. The ether extracts were treated with decolorizing charcoal and silica gel and then filtered through silica gel over Celite. The contents of the funnel were washed with ether, and white crystals were collected by concentration: (9.98 g, 87.3%), mp 151-152°C; IR (KBr) 1655 cm^{-1} (C=O), 3300 cm^{-1} (NH). NMR ($CDCl_3$) δ 0.93 (s, 3H); 1.14-1.63 (m, 24H); 2.35-2.41 (m, 4H); 2.75 (br s, 1H); 3.05-3.24 (m, 3H); 3.60-3.73 (d, 1H); 4.7 (br s, 1H).

Anal. Calcd for $C_{19}H_{37}N_3S_2O$: C, 58.89; H, 9.62; N, 10.84; S, 16.54.
Found: C, 59.27; H, 9.35; N, 11.20; S, 16.93.

Preparation of 2,2,6,6,9,9-hexamethyl-4,7-diaza-4-piperidinyl-ethyl-1,10-decanedithiol (5)

In a freshly-dried 250 ml round bottom flask, **4** (7.50 g, 0.1934 mole) was dissolved in dry THF (80 ml). Lithium aluminum hydride (1.54 g, 0.04071 mole) was added over 2 min. After refluxing for 19 hr, the reaction was quenched with satd NH_4Cl. Volatiles were removed in vacuo (60°C). To the residue, absolute EtOH (100 ml) was added and the mixture was stirred for 2 hr. After filtration, the filtrate was evaporated to dryness (65°C) in vacuo. Water was added (50 ml), and the pH was adjusted to 5.0 with concentrated HCl. The pH was adjusted to 6 by adding 1*M* NaOH, and extracted with diethyl ether (50 ml/extraction) to remove ether soluble impurities. These ether solutions were discarded. The pH was then adjusted to 6.2-7.2 and extracted with fresh ether. These ether solutions were dried (Na_2SO_4), filtered, and the hydrochloride salt was made by addition of $HCl_{(g)}$. The salt (white solid, 4.35 g, 47.6%) was isolated by evaporation in vacuo at 45°C and dried overnight (25°C, < 5 mm Hg.) The salt is very hygroscopic, soluble in water and chlorinated solvents, heat sensitive, and migrates on TLC

TABLE 1
Biodistribution of Complex II and Complex III in Mice Average of Six Mice

	5 min		15 min		30 min	
COMPLEX II	%dose	%dose	%dose	%dose	%dose	%dose
Organ	organ	g	organ	g	organ	g
Brain	2.19 ± 0.62	4.89 ± 1.63	1.01 ± 0.17	2.31 ± 0.45	0.53 ± 0.07	1.22 ± 0.20
Total blood	2.04 ± 0.44	0.92 ± 0.22	0.99 ± 0.16	0.44 ± 0.07	0.88 ± 0.16	0.40 ± 0.07
Heart	0.86 ± 0.27	6.27 ± 2.26	0.54 ± 0.09	3.93 ± 0.82	0.35 ± 0.08	2.67 ± 0.61
Lung	4.87 ± 1.62	15.85 ± 4.78	1.85 ± 0.40	7.78 ± 1.72	1.35 ± 0.25	6.46 ± 1.42
Liver	17.15 ± 2.30	9.80 ± 1.04	22.45 ± 2.05	12.65 ± 0.91	26.29 ± 3.03	15.70 ± 0.98
Kidney	6.15 ± 1.19	3.69 ± 2.16	2.79 ± 0.62	6.11 ± 1.05	2.50 ± 0.54	5.30 ± 0.63
Spleen	0.58 ± 0.14	5.29 ± 0.08	0.46 ± 0.07	4.27 ± 0.86	0.33 ± 0.06	3.18 ± 0.39
Stomach	3.50 ± 0.83		3.80 ± 0.58		3.83 ± 2.35	
GI tract	25.11 ± 3.45		30.18 ± 3.71		42.76 ± 6.33	
Brain / Blood		5.32		5.19		3.00
COMPLEX II						
Brain	1.09 ± 0.31	2.48 ± 0.74	0.28 ± 0.09	0.61 ± 0.19	0.16 ± 0.67	0.35 ± 0.15
Total blood	2.52 ± 0.89	1.04 ± 0.34	1.29 ± 0.42	0.50 ± 0.14	0.83 ± 0.30	0.34 ± 0.16
Heart	0.40 ± 0.12	2.88 ± 0.75	0.18 ± 0.06	1.20 ± 0.45	0.13 ± 0.06	0.85 ± 0.38
Lung	1.65 ± 0.48	7.00 ± 1.74	0.63 ± 0.09	2.84 ± 0.57	0.52 ± 0.15	2.18 ± 0.52
Liver	19.15 ± 1.61	12.47 ± 1.14	19.29 ± 5.25	11.26 ± 2.58	22.76 ± 5.90	13.47 ± 3.35
Kidney	4.46 ± 1.34	9.14 ± 2.49	2.95 ± 1.99	5.36 ± 2.38	1.94 ± 0.53	3.87 ± 1.16
Spleen	0.32 ± 0.08	3.44 ± 0.85	0.14 ± 0.05	1.41 ± 0.56	0.11 ± 0.05	1.00 ± 0.38
Stomach	2.39 ± 0.52		2.30 ± 0.63		2.16 ± 0.82	
GI tract	14.91 ± 2.09		23.00 ± 7.30		35.26 ± 7.83	
Brain / Blood		2.40		1.20		1.02

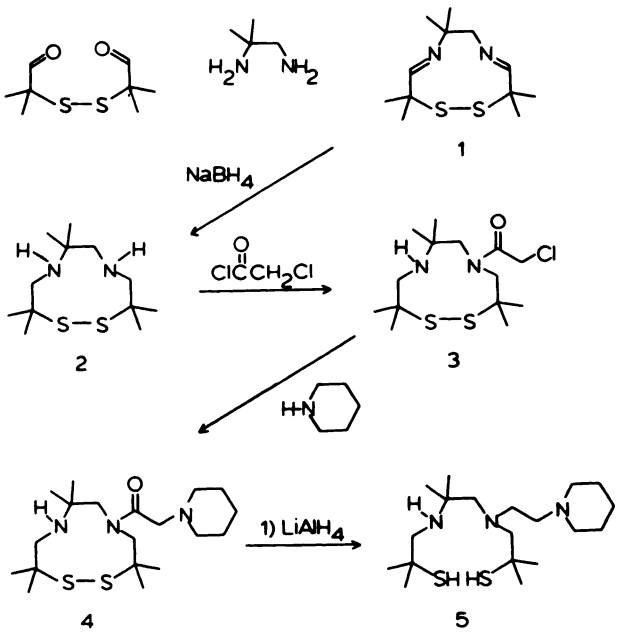

FIGURE 4
Triaminedithiol ligand synthesis

(alumina/1:1 pentane/ether: R_f 0.62, positive with Ellman's Reagent). IR (free base) 3,300 cm^{-1} (NH). NMR (D_2O) δ 1.44, 1.46, 1.48 (3s, 18 H); 1.74 (m, 6H); 2.84 (s, 2H); 3.06, 3.12 (2s, 4H); 3.20, 3.31, 3.35 (m, 6H).

Anal. Calcd for $C_{19}H_{41}N_3S_2 \cdot HCl \cdot 1\ 1/2\ H_2O$: C, 48.17; H, 9.57; N, 8.87; S, 13.54; Cl, 14.97.
Found: C, 48.17; H, 9.47; N, 8.86; S, 13.47; Cl, 15.04.

Radiolabeling

Sodium [^{99m}Tc]pertechnetate (5-30 mCi in 0.1 to 0.3 ml of saline) eluted from a ^{99}Mo → ^{99m}Tc generator,‡‡ 1.0 mg ligand (5), and 0.4 ml phosphate buffer (pH 7.0—0.029*M* NaOH and 0.05*M* KH_2PO_4) was vortexed and kept at room temperature for 10 min. A freshly prepared solution of $SnCl_2 \cdot 2H_2O$ (0.1 ml, 1.33 × 10^{-4}*M* in absolute ethanol) was added to this solution. The reaction mixture was vortexed and kept at room temperature for 30 min. The reaction mixture was analyzed by liquid chromatography using mixtures of ethanol and 0.01*M* aqueous NH_4OAc and a radioactivity detector. With a solvent mixture at 2 ml/min flow rate of 45% EtOH/55% 0.01*M* aqueous NH_4OAc, three radioactive components were detected. At these conditions, excess ligand, monitored by ultraviolet detection at 220 nm, was shown to be separated from the radioactive peaks. The major radioactive peaks were collected by way of preparative chromatography. For mouse studies, the eluant was diluted with saline to prepare a 10 μCi/ml solution. The resultant solution contained < 0.1% EtOH. For primates, the eluant was evaporated without heat under reduced pressure to dryness and redissolved in saline. The solution was passed through a 0.22 μ filter directly into a clini-chem vial. Prior to studies, the samples were re-analyzed by HPLC, and determined to be > 98% pure.

BIODISTRIBUTION STUDIES

Mice

Nonfasted male CD1 mice weighing 32-37 g were each injected intravenously with purified ^{99m}Tc complex (0.1 ml, 1 μCi, ~ 3 pg) through the tail vein. At different time periods (5 min, 15 min, 30 min) after injection the mice were lightly etherized, killed by decapitation, and blood (0.1 ml) immediately collected. The organs of interest were excised, weighed, and their radioactive content determined in an auto gamma counter.

The % injected dose/organ was determined by comparison of tissue radioactivity levels with suitably diluted aliquots of the injectant solution; the %dose/g of wet tissue was calculated by dividing the %injected dose/organ by the actual organ weight. The brain-to-blood ratios were calculated from the %dose/g of wet tissue and %dose/g of blood. Results are presented in Table 1.

Primates

Two primate imaging studies were carried out. The first subject was an adult female cynamologous monkey anes-

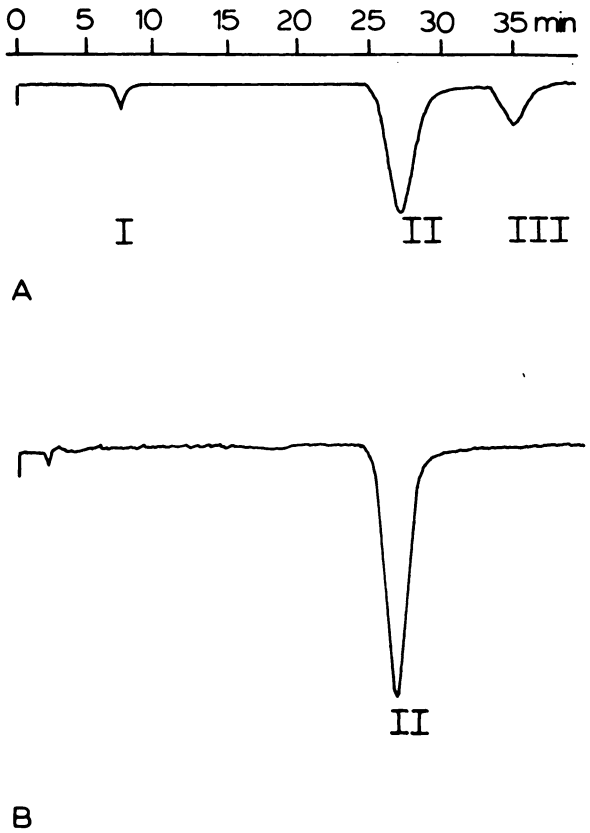

FIGURE 5
HPLC traces of A: crude ^{99m}Tc reaction mixture; and B: purified complex used for primate studies

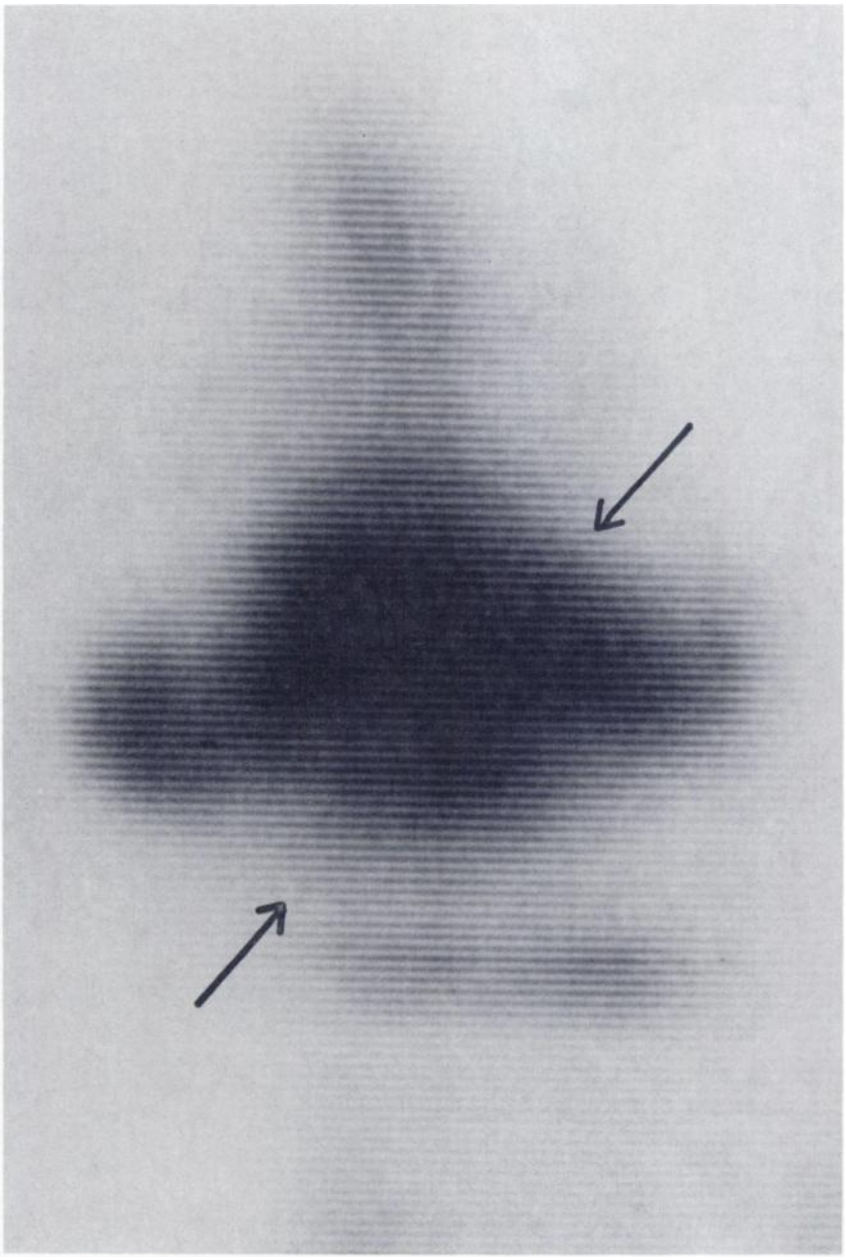

FIGURE 6
Vertex view of cynamologous monkey at 5–10 min postinjection with lower body shielding showing brain uptake

thetized with 200-300 mg total ketamine. The chosen purified ^{99m}Tc complex (7 mCi) was injected into a peripheral hind limb vein and imaged on a gamma camera[¶¶] interfaced to a computer.*** An adult male baboon, anesthetized with 200 mg ketamine and maintained by 2% suritol through the course of the study, was imaged following the injection of 14 mCi of the purified complex into a peripheral limb vein with a gamma camera[†††] interfaced to a computer.[‡‡‡] Multiple images in the vertex position were obtained with an increasing frame rate up through 40 min in the monkey, and 75 min in the baboon. Subsequently, lateral views were obtained at the end of the studies. Individual frames were quantified from regions of interest over the brain to generate time-activity curves. The curves were decay corrected for both primates.

RESULTS

Organic chemistry

The ligand was made as shown in Fig. 4. The macrocyclic diamine **1** was formed by condensation of the dialdehyde and diamine (*11*). Reduction with sodium borohydride gave the diaminedisulfide **2** which was acylated in high yield with chloroacetyl chloride to give **3**. Displacement of the chlorine by piperidine afforded the aminoamide **4**. Reduction of the amide and concomitant cleavage of the disulfide bond was accomplished by reaction with excess lithium aluminum hydride. The resulting N-piperidinylethyl-diaminedithiol **5** was isolated as the di-HCl salt, and gave appropriate physical data.

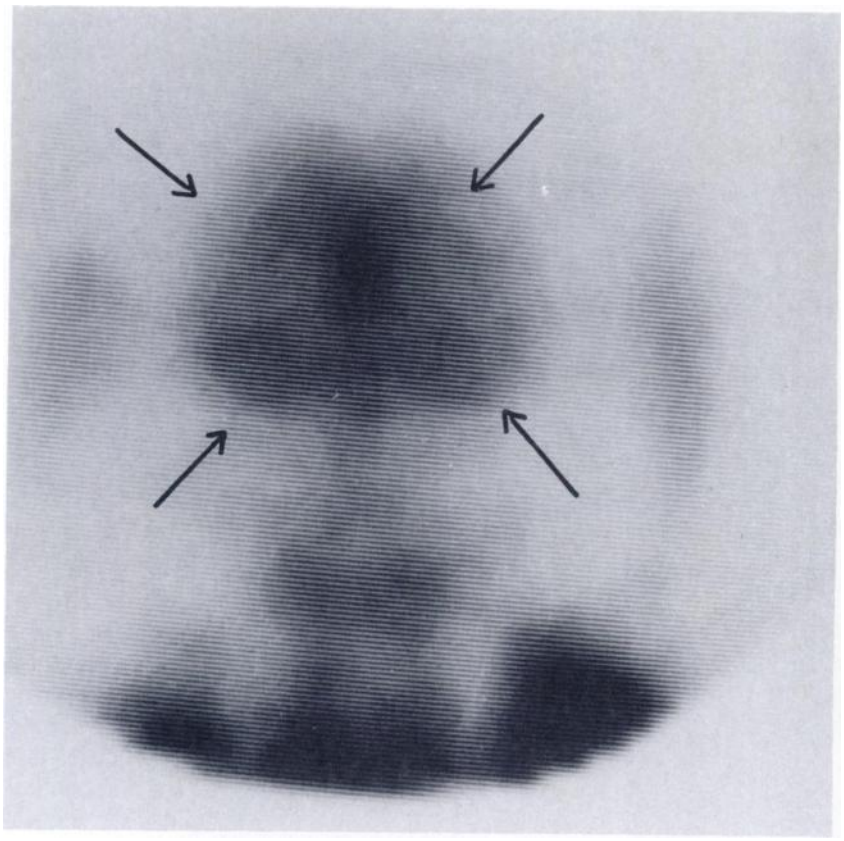

FIGURE 7
Vertex view of baboon at 5–10 min postinjection with lower body shielding showing brain uptake

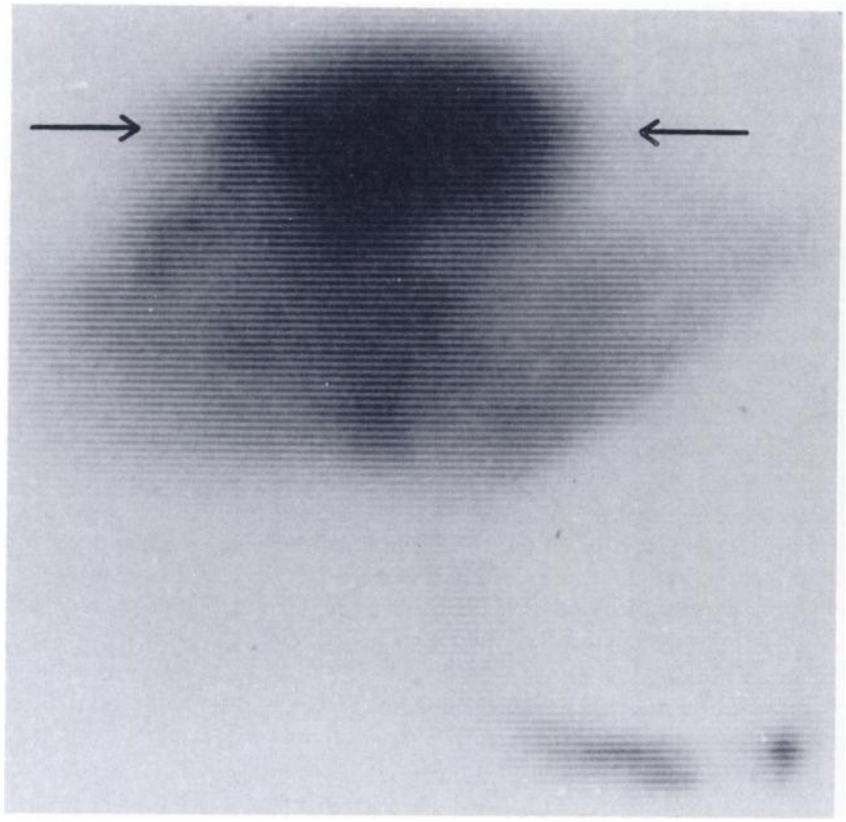

FIGURE 8
Lateral view of monkey at 40 min postinjection

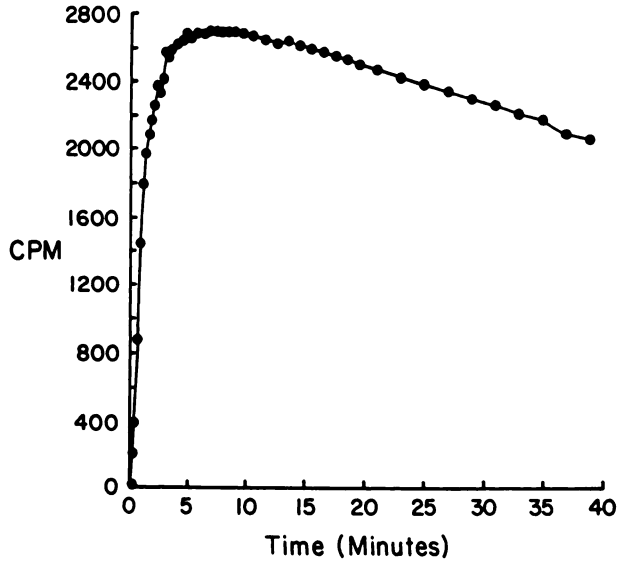

FIGURE 9
Time-activity curve of ^{99m}Tc complex in cynamologous monkey brain

Radiochemistry

The ^{99m}Tc complex was prepared by mixing the ligand with ~ 5-30 mCi $Na^{99m}TcO_4^-$ in phosphate buffer (pH 7.0) as described. Analysis and purity assessment was accomplished by HPLC. The reaction mixture showed three components: Peak I, a small peak which corresponded to the nonsubstituted hexamethyl ^{99m}Tc complex; and two major complexes represented by peaks II and III which eluted at longer retention times (Fig. 5.) Complexes II and III were formed in an 80:20 ratio. Each peak was isolated through preparative chromatography, and shown to be stable in a separate experiment for at least 24 hr. Samples injected into the mice or primates were greater than 98% pure and injected less than 1 hr after isolation.

Biodistribution

Mice

The more promising of the two ^{99m}Tc complexes was Complex II with 2.2% of the injected dose in the brain at 5 min postinjection. The brain-to-blood ratio was 5.3 at 5 min and 3.0 at 30 min, suggesting sufficient uptake and retention time in the brain for imaging humans, provided the biodistribution is similar.

Primates

The cynamologous monkey and baboon were injected with purified ^{99m}Tc complex II (7 mCi and 14 mCi, respectively). High brain uptake is seen in the 5 to 10 min vertex views of the monkey (Fig. 6) and baboon (Fig. 7). There is still considerable uptake at 40 min postinjection as seen in the lateral view of the monkey (Fig. 8). Each of the time activity curves (Figs. 9 and 10) showed an initial rapid rise with the plateau about 11 min in length (6-16 min). Washout curves gave $T_{1/2}$ values at 63 min and 58 min, respectively, calculated from the maximum value.

DISCUSSION

A new ligand, N-piperidinylethyl-DADT, has been prepared which has a piperidinylethyl side chain attached to the less sterically hindered nitrogen atom of a hexamethyl-DADT ligand. The synthetic route used to prepare this compound is quite versatile and allows for the straightforward synthesis of analogs of N-piperidinylethyl-DADT which possess a variety of amine substituents on the side chains as well as permitting the length of the alkyl group separating the amino-substituent from the DADT backbone to be varied. Eight such ligands have been prepared by this route and will be reported on in a future publication. N-piperidinylethyl-DADT **5** forms two complexes (Complex II and Complex III) with ^{99m}Tc when pertechnetate ion is reduced with stannous chloride in an aqueous, phosphate buffered solution of the ligand. These complexes can be easily separated by reverse phase HPLC and are stable in solution for at least 24 hr (data not shown). Saline solutions containing < 0.1% ethanol for animal studies of each of these complexes can be prepared either by diluting the HPLC eluant with saline or by evaporating the eluant to dryness and redissolving the purified complex in saline. Re-analysis of these solutions by HPLC prior to use in animal studies demonstrated that the complexes were >98% pure.

The confirmation that the structure for Complex II is as shown rests on the synthesis of the complexes on the ^{99}Tc level. To this date, initial results based on the complexes formed on the ^{99}Tc level show that the complexes have identical retention times by HPLC. Physical and analyti-

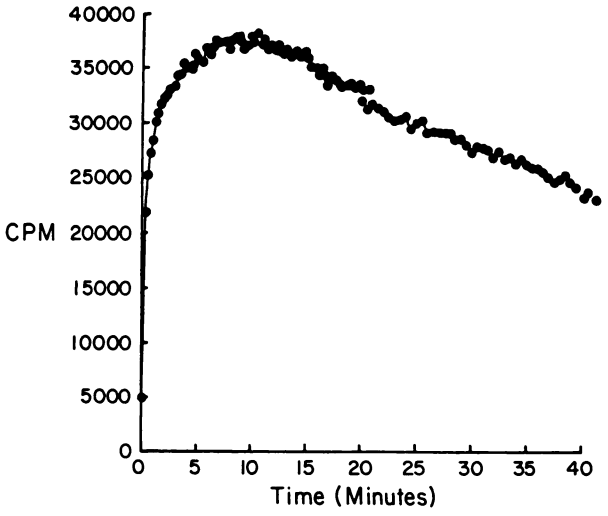

FIGURE 10
Time-activity curve of ^{99m}Tc complex in baboon brain

cal data gathered to date support the structure as formulated in Fig. 3. Full characterization will follow in a future publication. Biodistribution studies of both of these complexes have been conducted in mice. These studies show that at 5 min postintravenous injection of Complex II 2.2% of the injected dose is in the brain of the mouse with 0.53% of the dose remaining in the brain after 30 min. The brain-to-blood ratios at these times were 5.3 and 3.0, respectively. Similar studies with Complex III showed somewhat lower, but still significant, brain uptake and retention.

Imaging studies with Complex II in a cynamologous monkey and a baboon showed rapid uptake of the complex in the brain of both animals with the peak accumulation of the tracer in the brain occurring at ~ 5 to 7 min post i.v. injection. A plateau of about 11 min was observed in both animals (Figs. 8 and 9). Brain washout curves of 63 min and 58 min were obtained for the monkey and baboon respectively. These results suggest that [^{99m}Tc] N-piperidinylethyl-DADT may be useful for either planar or single photon emission computed tomographic imaging of the brain in humans.

FOOTNOTES

* Hoover Mel-Temp., Limerick, PA.
† IBM NR/80F, White Plains, NY.
‡ Perkin Elmer 399B, Perkin Elmer Corp., Pomono, CA.
§ Atlantic Microlabs, Atlanta, GA.
¶ Perkin-Elmer Series 2, Perkin Elmer Corp., Pomono, CA.
** Waters Novapak, Waters Chromatography, Milford, MA.
†† Perkin Elmer LC-75 Autocontrol, Perkin Elmer Corp., Pomono, CA.
‡‡ Cintichem and Union Carbide, Danbury, CT.
§§ Packard Tri-Carb., Packard Instrument Co., Downers Grove, IL.
¶¶ Searle-Siemens Medical Systems, Inc., Iselin, NJ.
*** Informatek Simis 3, Sopha Medical Systems, Baltimore, MD.
††† Toshiba Medical Systems, Tustin, GA.
‡‡‡ Technicare VIP 560, Technicare, Solon, OH.

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